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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/719,571	09/25/96	ANDERSON D	A-63899-1

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EXAMINER	
GRUN, J	
ART UNIT	**PAPER NUMBER**
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/719,571	ANDERSON
Examiner	**Group Art Unit**
James L. Grun, Ph.D.	1645

☒ Responsive to communication(s) filed on *08 Sept 1997 and 29 Sept 1997* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-14* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-14* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948. substitute

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4 and 5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948 substitute

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Effective 07 February 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center 1600, Group 1640, Art Unit 1645.

This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed. When formal drawings are submitted, the draftsperson will perform a review. Direct any inquiries concerning drawing review to the Drawing Review Branch at (703) 305-8404

The disclosure is objected to because of the following informalities: the specification is replete with spelling errors too numerous to mention specifically, e.g.: page 6, line 5, --enrichment-- is misspelled; page 6, line 16, --bodies-- is misspelled; page 12, line 1, --Neurofilaments-- is misspelled; page 17, line 16, --similar-- is misspelled; page 31, line 15, --avian-- is misspelled; etc. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide description of or enablement for any and every antibody population specific for a RET protein or for the extracellular domain thereof other than antibodies 3A61D7, 3A61C6, or 2C42H1 (see pages 9 and 18). Applicant provides guidance for the above noted monoclonal antibodies and provides no guidance as to what modifications or structure are important for the predictable function of any other monospecific antibody. Very different structures may be found on antibodies with the same specificity. For example, very different V_H chains can combine with the same V_L chain to produce antibody binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_L sequences to produce antibodies with very similar properties. These observations indicate that divergent variable region sequences, both in and out of complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. Conversely, similar structure may be found on antibodies having different specificities. In the absence of any guidance other than to the use of the 3A61D7, 3A61C6, or 2C42H1 antibodies, one would not know or be able to predict what structure or modifications were important and the amount of experimentation required to determine same would be undue.

Moreover, absent further guidance from Applicant, one would not be assured of the ability to obtain antibodies which bind to other than mouse or rat RET proteins. Note that an enabling disclosure for the preparation and use of only a few analogs of a product does not enable all possible analogs where the characteristics of the analogs are unpredictable. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd. (18 USPQ 2d 1027 (CAFC 1991)). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Should Applicant amend the anti-RET antibody claims to claim specific monoclonal antibody species, such claims would be rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are: (1) known and readily available to the public; (2) reproducible from the written description; or, (3) deposited in compliance with the criteria set forth in 37 CFR §§ 1.801-1.809.

It is unclear if cell lines which produce antibodies having the exact chemical identity and properties of the antibodies designated 3A61D7, 3A61C6, or 2C42H1 are known and publicly available, or can be reproducibly isolated without undue experimentation. Accordingly, filing of evidence of the reproducible production of the cell lines and antibodies necessary to practice the invention or filing of evidence of deposit is required. Without a publicly available deposit of the above cell lines, one of ordinary skill in the art could not be assured of the ability to practice the invention with such claimed antibody species. Exact replication of: a claimed cell line; cell lines

which produce chemically and functionally distinct antibodies as claimed; and/or, a claimed antibody's amino acid or nucleic acid sequence is an unpredictable event. As set forth above, very different structures may be found on antibodies with the same specificity, and conversely, similar structure may be found on antibodies having different specificities. Therefore, it would require undue experimentation to reproduce claimed monoclonal antibody species designated 3A61D7, 3A61C6, or 2C42H1. A suitable deposit of the hybridomas would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See the criteria set forth in 37 CFR §§ 1.801-1.809.

If the deposits are made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific cell lines have been deposited under the Budapest Treaty, that the cell lines will be irrevocably and without restriction or condition released to the public upon the issuance of a patent and that the cell lines will be replaced should they ever become non-viable, would satisfy the deposit requirement made herein.

If the deposits have not been made under the Budapest Treaty, then in order to certify that the deposits meet the criteria set forth in 37 CFR §§ 1.801-1.809, applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposits will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) the deposits were viable at the time of deposit; and,

(e) the deposits will be replaced if they should ever become non-viable.

Claims 8-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for RET+ cell populations from rat, and implicitly mouse, fetal gut, does not reasonably provide enablement for any and every neural progenitor cell population from any and

every animal species. Applicant does not describe or suggest a cell population other than those positive for RET antigen expression isolated from fetal gut of a rat with antibodies specific for mouse or rat RET. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Claims 4 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies specific for RET antigen expressed in mice and rats, does not reasonably provide enablement for any other reagent which specifically binds RET antigen. Applicant discloses only antibodies specific for RET antigen expressed in mice and rats and provides no description or guidance to any other reagent which specifically binds the RET antigen. Absent such guidance one would not know what other reagents function in the invention and would not know how to make same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Claims 1-7 and 12-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1-7 and 12-14, the metes and bounds of what is or is not encompassed by a "RET antigen" are entirely unclear.

In claim 7, --fluorochrome-- is misspelled.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-14 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Lo et al (Neuron 15: 527-539, 1995).

Lo et al (Neuron, 1995) disclose the invention essentially as claimed.

Claims 1-3 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Martucciello et al.

Martucciello et al disclose the Ret R5 monoclonal antibody, inherently produced by a hybridoma, which binds to the extracellular domain of Ret protein (see e.g. page 434, column 1).

Claims 8-11 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Stemple et al (Dev. Biol. 159: 12-23, 1993).

Stemple et al (1993; e.g. pages 17-19) disclose that a variety of substantially pure neural progenitor cell populations, fractionated by for example antigen expression, with a variety of developmental potentials were known to the art.

Claims 8-11 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Stemple et al (Cell 71: 973-985, 1992).

Stemple et al (1992) disclose fluorescence activated cell sorting for fractionation of neural stem cells of varying developmental potentials.

Claims 8-11 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Vescovi et al.

Vescovi et al disclose substantially pure neural progenitor cell populations with neuronal or glial developmental potential.

Claims 8-11 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Reynolds et al (Soc. Neurosci. Abstr. 18: 1107, Abstract 467.3, 1992).

Reynolds et al disclose substantially pure neural progenitor cell populations with neuronal or astrocyte developmental potential.

Claims 8-11 are rejected under 35 U.S.C. § 102(e) as being clearly anticipated by Boss et al (US 5,411,883).

Boss et al disclose and claim substantially pure neural progenitor cell populations.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> (c) Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-3 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hesketh in view of Martucciello et al, Campbell, Harlow et al, and Maurer et al.

Hesketh teaches the cellular location, tissue distribution, and amino acid sequence of RET.

Martucciello et al teach a variety of antibodies specific for epitopes of RET and their use for immunohistochemical localization of the protein.

Campbell teaches (page 29) that affinity purification uses of monoclonal antibodies are known tho the art and that "[i]t is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)."

Harlow et al teach that, once the amino acid and/or nucleic acid sequences of a protein are known, it is routine and conventional in the art to elicit antibodies to peptides and/or fusion proteins derived from the protein and/or to prepare a bank of site-specific monoclonal antibodies for a variety of uses such as functional and clinical studies (pages 72-77). Harlow et al further teach rationales for the selection of synthetic peptides as immunogens (pages 72-77).

Maurer et al teach that the method by which a protein or polypeptide immunogen is presented to a host can influence the ability of that immunogen preparation to elicit a response, i.e. by employing the correct "carrier" and conjugation procedure for a protein or polypeptide, an immune response to almost any macromolecule (even those believed to be nonimmunogenic) can be elicited (page 50). Further, the reference teaches typical methods for the production of both polyclonal and monoclonal antibodies (pages 64-67).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have elicited antibodies to any epitope of a RET protein sequence as disclosed by Hesketh because the RET protein is of unquestioned research interest, it is conventional in the art to elicit antibodies to sequenced proteins for a variety of uses as taught in any of Martucciello et al, Campbell, or Harlow et al, and one of ordinary skill in the art would have had an extremely

reasonable expectation of success in achieving the expected result, i.e. generating antibodies, either polyclonal or monoclonal antibodies specifically reactive with any of the variety of specific epitopes in a RET protein, using immunogens derived from the sequences of the RET protein, taught in Hesketh, in view of the known immunogenicity of RET as suggested by the ability to elicit the antibodies of Martucciello et al, in conjunction with notoriously old and well known conventional techniques as taught by Harlow et al and Maurer et al. See Ex parte Erlich (3 USPQ2d 1011 (BPAI 1987)). It would have been obvious to have generated monoclonal antibodies in order to provide a potentially unlimited source of homogeneous reagent for uses such as affinity purification, functional studies, or clinical studies of the protein and its expression. It would have been obvious to have provided any of the conventional detectable labels on the antibodies as such labelling is conventional in the art for, inter alia, detection of antibody binding.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claims 4-14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lo et al (Perspectives Dev. Neurobiol. 2: 191-201, 1994), Stemple et al (Dev. Biol. 159: 12-23, 1993), Stemple et al (Cell 71: 973-985, 1992), and Martucciello et al.

Lo et al teach the expression of, inter alia, the gene encoding RET as a valuable marker for very early stages in neural crest cell lineage diversification and suggest the isolation and culture of cells expressing the marker for further testing of developmental potential (e.g. pages 199-200).

Stemple et al (Dev. Biol., 1993) teach developmental heterogeneity in neural crest cell derived populations and that analysis of environmental factors in combination with clonal analysis and/or immunological subfractionation (i.e. using antibodies to cell-surface antigens to purify antigen-positive or antigen-negative populations for culture) have provided and will provide further valuable information toward understanding cell lineage decisions, proliferation, and/or survival of such cell populations (see e.g. pages 16-21).

Stemple et al (Cell 71: 973-985, 1992) disclose fluorescence activated cell sorting for fractionation of neural stem cells of varying developmental potentials.

Martucciello et al teach RET as a transmembrane protein (page 433) and disclose the Ret R5 monoclonal antibody, implicitly produced by a hybridoma, which binds to the extracellular domain of RET protein (see e.g. page 434, column 1).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have used antibodies, such as those of Martucciello et al, for the immunological fractionation of RET+ cells by conventional methods for the isolation of such cells, such as fluorescence activated cell sorting as taught in Stemple et al (Cell, 1992), because Stemple et al (Dev. Biol., 1993) teach that, inter alia, immunological subfractionation of progenitor cells was known to provide valuable information toward understanding cell lineage decisions, proliferation, and/or survival of such cell populations, and Lo et al specifically teach RET as a valuable marker for very early stages in neural crest cell lineage diversification and specifically suggest that cells expressing this marker should be isolated for further testing. One of ordinary skill in the art would have had an

extremely reasonable expectation that the conventional methods taught by the references would function as desired and provide the desired cell population enriched for the desired expressed marker.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Tsuzuki et al disclose immunological detection of RET in tissues of neural crest origin.

Nakamura et al disclose immunological detection of RET in tissues of neural crest origin.

Pachnis et al teach the expression of the gene encoding RET during mouse embryogenesis.

Davis et al disclose substantially pure neural stem cell populations with varied developmental potentials.

Deville et al (1992) disclose substantially pure neural stem cell populations with varied developmental potentials.

Deville et al (1994) disclose substantially pure neural stem cell populations with varied developmental potentials.

Duff et al disclose substantially pure neural stem cell populations with varied developmental potentials.

Hall et al disclose substantially pure neural stem cell populations with varied developmental potentials.

Ito et al disclose substantially pure neural stem cell populations with varied developmental potentials.

Le Douarin et al (1991) disclose (e.g. pages 182-183) substantially pure neural stem cell populations with varied developmental potentials.

Morshead et al disclose substantially pure neural stem cell populations with varied developmental potentials.

Reynolds et al (Science, 1992) disclose substantially pure neural stem cell populations with varied developmental potentials.

Sieber-Blum et al (1980) disclose substantially pure neural stem cell populations with varied developmental potentials.

Temple discloses substantially pure neural stem cell populations with varied developmental potentials.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (703) 308-3980. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula K. Hutzell, Ph.D., can be reached on (703) 308-4310. The fax phone numbers for official communications to Group 1640 are (703) 305-3014 or (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

James L. Grun, Ph.D.
March 30, 1998

CAROL A. SPIEGEL
PRIMARY EXAMINER
GROUP ~~1800~~ 1600